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Cover Art: Two paintings of horse heart cytochrome *c* by Irving Geis in which the protein is illuminated by its single iron atom. On the front cover the hydrophilic side chains are drawn in green, and on the back cover the hydrophobic side chains are drawn in orange. The paintings are based on an X-ray structure by Richard Dickerson.

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C. Classification and Characteristics

The most common and perhaps the most useful way of classifying the 20 "standard" amino acids is according to the polarities of their side chains (**R groups**). This is because proteins fold to their native conformations largely in response to the tendency to remove their hydrophobic side chains from contact with water and to solvate their hydrophilic side chains (Chapters 7 and 8). According to this classification scheme, there are three major types of amino acids: (1) those with nonpolar R groups, (2) those with uncharged polar R groups, and (3) those with charged polar R groups.

The Nonpolar Amino Acid Side Chains Have a Variety of Shapes and Sizes

Nine amino acids are classified as having nonpolar side chains. **Glycine** (which, when it was found to be a component of gelatin in 1820, was the first amino acid to be identified in protein hydrolyzates) has the smallest possible side chain, an H atom. **Alanine, valine, leucine,** and **isoleucine** have aliphatic hydrocarbon side chains ranging in size from a methyl group for alanine to isomeric butyl groups for leucine and isoleucine. **Methionine** has a thiol ether side chain that resembles an *n*-butyl group in many of its physical properties (C and S have nearly equal electronegativities and S is about the size of a methylene group). **Proline**, a cyclic secondary amino acid, has conformational constraints imposed by the cyclic nature of its pyrrolidine side group, which is unique among the "standard" 20 amino acids. **Phenylalanine,** with its phenyl moiety, and **tryptophan** with its indole group, contain aromatic side groups, which are characterized by bulk as well as nonpolarity.

Uncharged Polar Side Chains Have Hydroxyl, Amide, or Thiol Groups

Six amino acids are commonly classified as having uncharged polar side chains. **Serine** and **threonine** bear hydroxylic R groups of different sizes. **Asparagine** and **glutamine** have amide-bearing side chains of different sizes. **Tyrosine** has a phenolic group, which, together with the aromatic groups of phenylalanine and tryptophan, accounts for most of the UV absorbance and fluoresence exhibited by proteins. **Cysteine** has a thiol group that is unique among the 20 amino acids in that it often forms a disulfide bond to another cysteine residue (Fig. 4-4) through the oxidation of their thiol groups. This dimeric compound is referred to in the older biochemical literature as the amino acid **cystine.** The disulfide bond has great importance in protein structure: *It can join separate polypeptide chains or cross-link two cysteines in the same chain.* The confusing similarity between the names cysteine and cystine has led to the former occasionally being referred to as a **half-cystine** residue. However, the realization that cystine arises through the cross-linking of two cysteine residues after polypeptide biosynthesis has occurred has caused the name cystine to become less commonly used.

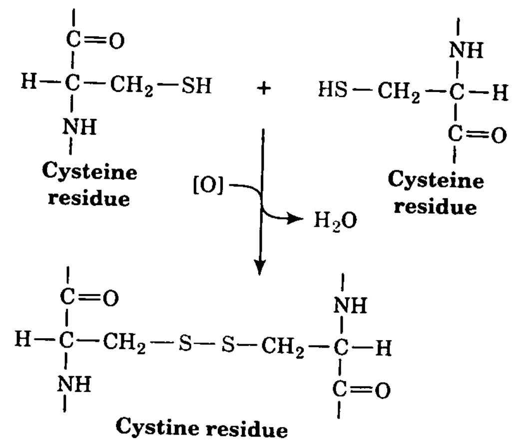

FIGURE 4-4. The cystine residue consists of two disulfide-linked cysteine residues.

Charged Polar Side Chains May Be Positively or Negatively Charged

Five amino acids have charged side chains. The basic amino acids are positively charged at physiological pH values; they are **lysine**, which has a butylammonium side chain, **arginine**, which bears a guanidino group, and **histidine**, which carries an imidazolium moiety. Of the 20 α-amino acids, only histidine, with $pK_R = 6.0$, ionizes within the physiological pH range. At pH 6.0, its imidazole side group is only 50% charged so that histidine is neutral at the basic end of the physiological pH range. As a consequence, histidine side chains often participate in the catalytic reactions of enzymes. The acidic amino acids, **aspartic acid** and **glutamic acid**, are negatively charged above pH 3; in their ionized state, they are often referred to as **aspartate** and **glutamate.** Asparagine and glutamine are, respectively, the amides of aspartic acid and glutamic acid.

The allocation of the 20 amino acids among the three different groups is, of course, rather arbitrary. For example, glycine and alanine, the smallest of the amino acids, and tryptophan, with its heterocyclic ring, might just as well be classified as uncharged polar amino acids. Similarly, tyrosine and cysteine, with their ionizable side chains, might also be thought of as charged polar amino acids, particularly at higher pH values, whereas asparagine and glutamine are nearly as polar as their corresponding carboxylates, aspartate and glutamate.

The 20 amino acids vary considerably in their physicochemical properties such as polarity, acidity, basicity, aromaticity, bulk, conformational flexibility, ability to cross-link, ability to hydrogen bond, and chemical reactivity. These several characteristics, many of which are interrelated, are largely responsible for proteins' great range of properties.